PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 002441.00175	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/036009	International filing date *(day/month/year)* 11 October 2005 (11.10.2005)	Priority date *(day/month/year)* 08 October 2004 (08.10.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS VACCINES AND DIAGNOSTICS INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 11 April 2007 (11.04.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Athina Nickitas-Etienne e-mail: pt04.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/036009	11.10.2005	08.10.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/315 A61K39/09 A61K39/40

Applicant
CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Mauhin, Viviane

Telephone No. +49 89 2399-7027

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/036009

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/036009

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-40 (all partially)

because:

☒ the said international application, or the said claims Nos. 37,38 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-40 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/036009

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. Invention 1: claims 1-40 (all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-19,34,35,39,40
	No:	Claims	1-9,20-33,36-38
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-36,39,40
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Claims 37 and 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

It is to be noted that following GAS proteins have not been searched: GAS313, SPY0274, SPY0731, GAS254, 286, 287, 288, 320, 321, 317, 293, 307, 308, 295, 310, 311, 312, , 300, 301, 313, 302, 304, 306, 303, 323, 328, 325, 330, 331, 322, 326, 324, 329, 332, 255, 260, 261, 334, 318, 281, 346, 350, 352, 355, protein F2-like protein of Table 11, the proteins of Table 13 which cannot be clearly identified as those cited in Table 12, SPY086 and GAS593 because they are not sufficiently characterized, i.e. no sequence identified by a Sequence Identity Number or no reference to a specific sequence is given in the application (Articles 5 and 6 PCT). They are thus not listed in the inventions below.

The separate inventions/groups of inventions are:

Inventions 1-68: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 2 in the apparition order in said Table 2, i.e. GAS antigen 5, 6, 18, 22, 23, 25, 29, 30, 36, 49, 56, 60, 62, 63, 65, 67, 68, 69, 74, 75, 76, 77, 78, 81, 82, 85, 86, 89, 91, 92, 93, 94, 96, 97, 98, 99, 100, 101, 103, 104, 105, 108, 123, 131, 142, 143, 158, 165, 166, 175, 178, 179, 187, 188, 190, 195, 205, 206, 207, 218, 219, 242, 249, 271, 291, 327, 380, 685, respectively, as well as to fragments and homologues of said sequences (e.g. GRAB precursor and SPs1285 of Table 11) and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 69-73: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 3 not mentioned in Table 2, in the apparition order in said Table 3, i.e. GAS 73, 74, 109, 129, 130, respectively, as well as to fragments and homologues of said sequence and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Invention 74: claims 1-40 (all partially)
Subject-matter relating to one of the GAS40 protein, in native form or as fusion protein as found in Table 4A-R as well as to fragments and homologues thereof (e.g. as found in Table 5), and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 75-137: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 7 not previously mentioned, in the apparition order in said Table 7, i.e. GAS 4, 15, 16, 24, 54, 57, 64, 72, 84, 102, 152, 157, 163, 168, 177, 191, 192, 193, 194, 198, 201, 224, 251, 259, 262, 264, 268, 277, 282, 299, 382, 405, 406, 425, 433, 460, 469, 493, 500, 545, 558, 587, 645, 650, 362-1, SPY0080a, 0272, 0461, 0611, 0717, 0792, 1029, 1073, 1260, 1613, 1835, 2005, 2093, 2178, GAS45, SPY0047, 0127, 0686, respectively, as well as to fragments and homologues thereof (e.g. M protein type 3 and C5A peptidase precursor of Table 11) and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 138-160: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 8 not previously mentioned, in the apparition order in said Table 8, i.e. GAS10, 83, 160, 284, 286, 292, 396, SPY0053, 0056, 0063, 0069, 0098, 0666, 0688, 0913, 1200, 1281, 1721, 1750, 1805, 2070, 2092 and g-21909751, respectively, as well as to fragments and homologues thereof and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 161-162: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 9 not mentioned previously, in the apparition order in said Table 9, i.e. NT01SP0246 and GAS309, respectively, as well as to fragments and homologues thereof and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 163-165: claims 1-40 (all partially)
Subject-matter relating to GAS proteins listed in Table 11 not mentioned previously in apparition order in said Table 11, i.e. SPY1664, GAS149 and SPY0861, respectively, and to fragments and homologues thereof (e.g. putative penicillin binding proteins 2X, putative large conductance mechanosensitive channel and hypothetical protein SPs1270 found in Table 11), and to the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 166-180: claims 1-40 (all partially)
Subject-matter relating to the proteins listed in Table 12 considering the references given.

Inventions 181-207: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins listed in Table 15 not mentioned previously in the apparition order in said Table 15, i.e. GAS35, 414, 426, 434, 437, 438, 439, 461, 465, 472, 473, 475, 477, 478, 495, 538, 543, 553, 561, 576, 577, 591, 592, 636, 643, 649, 663, respectively, as well as to fragments and homologues thereof, the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 208-236: claims 1-40 (all partially)
Subject-matter relating to the GAS proteins listed in Table 16 not mentioned previously in apparition order of said Table 16, i.e. GAS42, GAS95, M30098, M3_0100, M3_0102, M3_0104, SPs0106, GAS130, GAS137, M6_0157, M6_0159, GAS159, M6_0160, GAS217, 220, 290, 294, 384, 504, 509, 511, 527, 529, 533, 680, 19224134, 19224135, 19224137, 19224141, respectively, as well as to fragments and homologues thereof, the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 237-272: claims 1-40 (all partially)
Subject-matter relating to one of the GAS proteins not previously mentioned in the Tables but cited in the claims, in the apparition order in said claims, i.e. NT01SP0102, NT01SP0908 (SPY1111), NT01SP0182 (SPY0216), GAS70, 421, 428, 457, 474, 486, 492, 494, 535, 540, 560, 564, 565, 574, 579, 586, 607, 609, 625, 626, 640, 653, 657, 39, 58, 236, 366, 372, 389, M protein, SagA, Sfb1, Shp, respectively, as well as to fragments and homologues thereof, the encoding nucleic acid sequences and antibodies directed to said proteins.

Inventions 273-275: claim 36, partially
Subject-matter relating to the use of an antibody in the manufacture of a medicament for treating S. pyogenes infection, wherein the antibody specifically binds to a surface-exposed GAS antigen which is shorter by at least one amino acid than a GAS protein listed in Table 1 which was not previously mentioned, i.e. GAS41, GAS183 and GAS202, respectively.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present application discloses an active agent of a composition selected from a) a surface-exposed Streptococcus pyogenes GAS antigen which is shorter by at least one amino acid than a GAS protein selected from a multitude of GAS proteins, b) a nucleic acid molecule which encodes said GAS antigen and c) an antibody which specifically binds to said GAS antigen. Thus, the problem underlying the present application can be seen as the provision of a GAS antigen exposed at the surface of Streptococcus pyogenes which can be used as an active agent in a composition. However, such a GAS antigen is already known from the prior art, see e.g WO2004/078907 and Olive et al., 2002, Vaccine 20, pp2816-2825 and Ferretti et al., 2001, PNAS 98, pp 4658-4663. Such knowledge destroys the linking unit between the different GAS antigens of the present application. Since no other technical feature can be distinguished, which in the light of the prior art could be regarded as a special common technical feature, the ISA is of the opinion that there is no single inventive concept underlying the plurality of different inventions in the sense of Rule 13.2 PCT.
Accordingly, only invention 1 as indicated above has been searched by the ISA and is examined.

Re Item V.

1. Reference is made to the following document:

D1: WO 2004/078907 A (INTERCELL AG; MEINKE, ANDREAS; NAGY, ESZTER; WINKLER, BIRGIT; GELBMANN) 16 September 2004 (2004-09-16)

D2: NAKAGAWA ICHIRO ET AL: "Genome sequence of an M3 strain of Streptococcus pyogenes reveals a large-scale genomic rearrangement in invasive strains and new insights into phage evolution." GENOME RESEARCH, vol. 13, no. 6a, June 2003 (2003-06), pages 1042-1055, XP002367632 ISSN: 1088-9051

D3: SMOOT J C ET AL: "Genome sequence and comparative microarray analysis of serotype M18 group A Streptococcus strains associated with acute rheumatic fever outbreaks" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 99, no. 7, 2 April 2002 (2002-04-02), pages 4668-4673, XP002267116 ISSN: 0027-8424

D4: BANKS D J ET AL: "PROGRESS TOWARD CHARACTERIZATION OF THE GROUP A STREPTOCOCCUS METAGENOME: COMPLETE GENOME SEQUENCE OF A MACROLIDE-RESISTANT SEROTYPE M6 STRAIN" JOURNAL OF INFECTIOUS DISEASES, CHICAGO, IL, US, vol. 190, no. 4, 15

August 2004 (2004-08-15), pages 727-738, XP008047099 ISSN: 0022-1899

2.1 D1 discloses among 95 different proteins a spy0019 protein of SEQ. ID. No. 152 which is 100% identical to present GAS5 of SEQ. ID. No. 2 (as taken from Table 1 of the present application). Said protein is probably secreted (see Table 1) and is thus exposed at the surface of the bacteria. Immunogenic fragments of said protein are disclosed (see page 24, lines 4-5 or Table 1). The encoding nucleic acid sequence of SEQ. ID. No. 2 is 100% identical to present GAS5 of SEQ. ID. No. 651 over the whole length of GAS5. Antibodies directed to said protein are disclosed (see page 31, line 31 - page 32, line 22). Pharmaceutical compositions comprising either said protein or fragments thereof or the encoding nucleic acid sequence(s) are disclosed, whereby such a pharmaceutical composition may comprise one or more antigens (see page 35, line 50 - page 37, line 28). It is mentioned that an effective vaccine should be composed of proteins or polypeptides which are expressed by all strains (see page 12, lines 15-16, and Example 5). In Table 3, it is shown that spy0019 is expressed in 50 different strains covering the M1, M89, M3, M28, M12, M81, M49, M94, M22, M25, M83 and M85 serotypes (see Example 5 and Figure 4A). A pharmaceutical composition comprising said antibodies directed to said protein is disclosed (see page 39, lines 16-30). Kits and medical uses of said compositions are disclosed on page 40, lines 8-22).

2.2 D2 discloses a SPS0015 SPYM3_0014 protein of a M3 strain of S. pyogenes which is 99,497% identical to present GAS5 protein.

2.3 D3 discloses a SPYM18_0020 protein of a M18 strain of S. pyogenes which is 99,497% identical to present GAS5.

2.4 D4 discloses a M6_SPY0017 protein of a M6 strain of S. pyogenes which is 99,497% identical to present GAS5.

3. Novelty (Article 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9, 20-33 and 36-38 is not new in the sense of Article 33(2) PCT.

3.1 Claim 1 relates to a composition comprising at least one active agent selected from
a) a GAS antigen which is shorter by at least one amino acid that a GAS5 protein and which comprises a surface-exposed domain of the GAS5 protein
b) a nucleic acid molecule which encodes said GAS antigen
c) an antibody which specifically binds to said GAS antigen.
Claim 1 is not novel over D1 (Article 33(2) PCT).

3.2 Dependent claims 2-9 and 20-30 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty, see document D1 and the corresponding passages cited in the search report.

3.3 Independent claim 36 relates to the use of an antibody directed to an antigen which is at least one amino acid shorter than the GAS5 protein.
In view of D1, claim 36 is not novel (Article 33(2) PCT).

3.4 Independent claim 31 relates to a method of making a vaccine comprising combining the active agent with a pharmaceutical acceptable carrier.
In view of D1, claim 31 is not novel (Article 33(2) PCT).

3.5 Dependent claim 32 does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of novelty, see document D1 and the corresponding passages cited in the search report.

3.6 Independent claim 33 relates to the use of two GAS antigens in the manufacture of a medicament for inducing immunity against S. pyogenes infection.
Claim 33 is not novel over D1 (Article 33(2) PCT).

3.7 Independent claims 37 and 38 relate to a method of treating a S. pyogenes infection comprising administrating to an individual an effective amount of a composition wherein the active agent is a polypeptide or nucleic acid, or an antibody, respectively.
Claims 37 and 38 are not novel over D1 (Article 33(2) PCT).

4. Inventive step (Article 33(3) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 10-19, 34, 35, 39 and 40 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1 D1 is regarded as being the closest prior art to the subject-matter of claim 10 or 11. The subject-matter of claims 10 or 11 differs from this known composition comprising at least two antigens in that at least one of the GAS antigen is expressed in M3 type GAS bacterium. The problem to be solved by the present invention may therefore be regarded as the provision of a further composition comprising at least two GAS antigens. The solution proposed in claims 10 or 11 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) because it is obvious to the skilled person to use a GAS5 antigen of another M type in view of D1 in the light of teaching of D2.

4.2 The same reasoning applies to the subject-matter of the claims 12 and 13 in view of D1 in the light of teaching of D4, thus claims 12 and 13 are also considered not inventive (Article 33(3) PCT).

4.3 The same reasoning applies to the subject-matter of the claims 16 and 17 in view of D1, thus claims 16 and 17 are also considered not inventive (Article 33(3) PCT).

4.4 Dependent claims 14, 15, 18 and 19 specify that the second antigen is of the M11 or M23 type (claim 14 or 18, respectively) whereby some possible antigens are listed in claim 15 or 19. The combination of a GAS5 antigen with an antigen of serotype M23 does not seem to have any particular effect or advantage compared to a combination with any other serotype as disclosed in D1. Thus claims 14, 15, 18 and 19 are not inventive (Article 33(3) PCT).

4.5 D1 is considered as the closest prior art to the subject-matter of independent claim 34. The subject-matter of claim 34 differs from the known use of one nucleic acid functionally encoding hyperimmune serum reactive antigens (see page 36, lines 9-16) in that the antigens shall be expressed in bacteria from different M types. The problem to be solved by the present invention may therefore be regarded as a further use of one acid nucleic encoding different antigens. The solution proposed in claim 34 of the present application cannot be considered as involving an inventive step (Article 33(3)

PCT) because it is obvious to the skilled person that the antigens used have to cover as much as possible serotypes as taught in D1.

4.6 A similar reasoning can be made for the use of two antibodies directed against two antigens that are expressed in bacteria of different M types. Thus, claim 35 does not meet the requirements of Article 33(3) PCT,

4.7 The kit claimed in claims 39 and 40 differs from the kits disclosed in D1 in that they comprise instructions for the methods claims in claims 37 and 38, respectively. The addition of instructions for the use of a known kit in a known method is trivial. Thus, claims 37 and 38 do not meet the requirements of Article 33(3) PCT.

5. Industrial applicability (Article 33(4) PCT)

Claims 1-36 and 39-40 meet the requirements of Article 33(4) PCT.